REMARKS/ARGUMENTS

With the entry of the current amendment:
Claims 1-16 are pending.
Claims 2-3 and 5-16 are cancelled with entry of this amendment.
Claims 17-23 are newly added with entry of this amendment.
Claims 1 and 4 are amended with entry of this amendment.

The substantive differences presented here are related to the amendments, in which the claims are amended to recite methods for identifying previously unidentified diet-regulated disease-associated polynucleotides using rodent strains, all of the same generation and all either male or virgin female, and wherein expression data is analyzed to identify genes in the disease susceptible strain wherein a gene that shows at least a two-fold increase or decrease in gene expression. Claim 1 has additionally been amended to incorporate the limitations of claim 2 (now cancelled) requiring that genes show to have at least a two-fold change in gene expression are matched with one or more independently-derived quantitative trait loci (QTLs) known to encode one or more genes that contribute to the development of a disease.

Most of the present rejections are identical to those presented earlier, and most of the applicant's rebuttals are also identical to those previously presented, so attention is directed to the previous office action response. The substantive differences presented here are related to the amendments.

Applicant has carefully considered the rejections, has discussed the matter with the examiner and has amended and narrowed the claims in view of the outstanding rejections. It is believed that the present claim limitations overcome the current 35 USC 112 rejections for enablement and written description, and reasonably shows that the applicant was in possession of the invention at the time of filing, since the application sets out actual data performed produced using in vivo rodent experiments.

The fact that the QTL's are known to be associated with actual diseases is hopefully sufficient to indicate utility of the identified genes. Additionally, this together with the fact that the matched genes show significantly altered expression in the disease-susceptible animals compared to the normal animals, should provide sufficient evidence that, in rodents, these genes are diet-regulated, disease associated genes.

The limitation requiring that the rodents all be of the same generation and all either male or virgin female should overcome the issue of variability amongst individuals due to sex or age.

The limitation requiring that the identified genes have at least a two-fold increase or decrease in gene expression in response to diet hopefully removes the issue of indefiniteness with regard to the measurable nature of the change in expression.

Remarks addressing Examiner's rejections in view of certain references

On February 1 2008, Examiner Sisson and the applicant's representative, Adam Bell, discussed the application. One of the items discussed was United States Patent 5,612,486 "Transgenic animals harboring APP allele having Swedish mutation" to McConlogue et al. This patent describes a rodent model for Alzheimer's disease. For the record, the applicant believes that this disclosure is not relevant to patentability as it does not describe or suggest certain key elements of the claims, including, in particular (1) methods for identifying previously unidentified diet-regulated disease-associated polynucleotides, and (2) dividing the two genotypically different cohorts into two groups, feeding each a different diet and measuring gene expression and comparing expression across the individuals that differ in either genotype or in diet. Neither does it suggest or describe matching the genes identified with quantitative trait loci. The applicant believes that these features are entirely novel.

Additionally, the examiner brought to the attention of the applicant the following references, requesting that the applicant distinguish the present invention from the combination of these references, especially in view of the obviousness standard.

6,020,143: Abstract, columns 17, 49, 53, 55, 60-61 describes the use of comparative (disease vs non disease) analyses that focuses on changes in the sequence, not expression, of a single gene.

Column 17: This section describes a comparison of genetic sequences between diseased and normal individuals. The change in sequence was not related to gene expression or to regulation by diet but rather, function of the gene product. The comparative approach used in the present application seeks to discover genes not previously associated with the disease process, the expression of which is diet-regulated and related to disease.

Column 49: This section describes a transgenic mouse model for Alzheimer's. The resulting comparisons practiced in this disclosure would be between mice which differ by one genetic change and any other genes contributing to the disease would be strain specific. A large body of evidence demonstrates that transgenes act differently in different genetic backgrounds. This differentiates our method from this referenced patent since we analyze differences between parental strains differing in many loci.

Column 53: describes the method for creating a transgenic mouse. This is not relevant to the present application.

Column 55: describes the use of a transgenic cell or transgenic animal to test for drug action on the presenilin gene. The target gene for drug action is known but at the time of its identification, its possible regulation by diet was not known.

Column 60 - 61 describes methods for the study of the interaction of a normal or mutant protein with interacting cellular components which were widely practiced at the time the reference was granted an allowance. They rely on a variety of technologies (BiaCore etc) to test protein-protein interactions in cell free system, or the yeast two hybrid system in a living cell. While comparisons between normal and mutant protein are used to determine proteins that may or may not interact, this section of the referenced patent describes analyses after the proteins are known.

Overall, this disclosure does not teach or suggest a method for identifying diet-regulated disease-associated genes.

6,426,340: Figure 1 describes data that examines the effect of a drug in different diets in Fisher 344 rats (one strain). This patent does not provide for differences in genetic makeups or how food might alter efficacy of drugs in different genetic makeups. - only the effect of the drug in different diets.

Column 4 and 5 describes drug treatments and specifically "...the at risk population of one or more of the mammals to be treated includes those (1) diagnosed with cancer or (2) having a close relative. Our application is distinguished from this reference since their method does not identify previously unidentified diet-regulated genes by analyzing gene expression in two strains.

6,384,087: columns 5, 8, and 9 describe the use of an agouti mouse with an additional aP2 gene to study the effect of calcium levels. Comparative methods are valuable for assessing differences between transgenic and normal mice, but this method is not designed to identify novel diet regulated genes that cause or contribute to disease.

The inventor believes that the following abstract, published after the applicant's priority date, will help in understanding the present invention and emphasizing the novelty and importance of the present method.

> Linder CC. ILAR J. 2006;47(2):132-40. Genetic variables that influence phenotype. Department of Natural Sciences, New Mexico Highlands University, Las Vegas, New Mexico, USA.
> Characterization of genetically engineered mice requires consideration of the gene of interest and the genetic background on which the mutation is maintained. A fundamental prerequisite to deciphering the genetic factors that influence the phenotype of a mutant mouse is an understanding of genetic nomenclature. Mutations and transgenes are often maintained on segregating or mixed backgrounds of often-unspecified origin. Minimizing the importance of strain and substrain differences, especially among 129 strains, can lead to poor experimental design or faulty interpretations of data. Genetic factors that influence phenotype can be categorized as traits that are unique to the background strain, unique to the gene of interest, or an interaction of both the background strain and the gene of interest. The commonly used inbred strains are generally well characterized and understood; however, specific genetic alterations combined with genes unique to the

> background inbred strain may lead to unexpected results. Genetic background effects can be analyzed and controlled for by using specific targeting and breeding strategies. Selection of appropriate experimental controls is critical. Ideally, mutations or transgenes should be characterized on more than one genetic background and in hybrids of the two progenitor strains. This approach may lead to the identification of novel genetic modifiers of the "gene of interest." Conditional mutagenesis technologies increase the options for controlling genetic background effects in addition to permitting the study of developmental and temporal changes in gene and protein expression and thus phenotype.

None of the above references suggest a method for identifying previously unidentified diet-regulated disease-associated polynucleotides. The references do describe methods for measuring gene expression in animals in a disease state, in animals that have a propensity for a disease, and in animals in response to diet, but none of the references identifies a previously unidentified diet-regulated disease-associated polynucleotide. Thus the claimed invention cannot be obvious since an essential component of the claimed invention is totally absent from any of the references.

None of the references suggest methods comparing expression across two cohorts, each divided into two groups where, each group is fed a different diet, and measuring gene expression and comparing expression across the individuals that differ in either genotype or in diet and then matching the genes shown above to have at least a two-fold increase or decrease in gene expression with one or more independently-derived quantitative trait loci (QTLs) known to encode one or more genes that contribute to the development of a disease. Once again, this element is missing, and although QTLs have certainly been known for many years, they have never been used with the other elements of claim 1 for identifying previously unidentified diet-regulated disease-associated polynucleotides, thus claim 1 cannot be obvious in view of the references.

As reasoned above, the above referenced do not disclose all the elements of the present invention, therefore the present invention cannot be obvious in light of the prior art disclosures. The art does disclose several common or similar elements and experimental techniques, some of which have been well known for many years, but the combination of these elements is not disclosed, and the fact that some of the elements were known does not make the invention obvious. Even if all the elements were known, the applicant asserts that the combination of

elements and the way in which they are combined to provide the invention would not have been obvious at the time of filing. Even now, several years after the disclosure of this method, an even though the inventor (a world authority on nutragenomics) has spoken widely on the subject, the adoption of the current techniques is slow and has met with resistance, since the novelty and unfamiliarity of the method provides a barrier for adoption. Nonetheless, as can be seen in the ILAR J. article, that the value of the present invention is gaining acceptance since it is seen to provide real and substantial benefits.

The following paragraph written by James Kaput, the inventor, and may help clarify exactly why it is so important to analyze gene expression in two strains with two different diets:

The fundamental thesis underlying genetic and environmental variability is that genes and chemicals from the environment interact uniquely in individuals. Hence, analyzing any one individual, or one genetic makeup of rodent, will necessarily lead to a result specific to that individual (or strain). Hence, the most important genes to identify are those that differ in expression between an individual (or strain) that is susceptible vs expression in an individual (or strain) that is not susceptible. a change in phenotype (disease vs normal) must be due to differences in gene expression by definition - that is, physiological differences are produced by changes in expression of genetic information. Since diet alters disease trajectory, diet must be regulating some of these genes but different individuals have different interactions between diet and genes. The comparative process is the key feature of the application, and to be inclusive of the factors that affect gene expression, one has to compare both genetic makeup and diet simultaneously.

Support for the amendments

The amendment to claim 1 is found in the original specification at:

> paragraph 77 ("Male or virgin female (eliminates complications and effects of pregnancy) mice of defined genotype are fed a semi-purified diet containing 4% corn oil for 1 wk...");

paragraph 53 ("Differential gene expression is identified between the compared groups, and genes are identified that show significant changes in expression (e.g., a 1.5 or 2.0 or 2.5 –fold increase or decrease in gene expression…");

paragraph 29 ("Genetic methods for identifying quantitative trait loci … have been developed over the past 15 years. Such methods identify regions of chromosomes encoding one or more genes that contribute to the development of a complex disease, e.g., diabetes");

and in originally filed claim 2.

Support for new claims 17 and 18 is found in claim 1. New claims 17 and 18 simply recite a narrower embodiment of claim 1.

Support for new claims 19 to 23 is found at:

paragraph 29 ("Approximately 1700 QTLs for diabetes, obesity, cancer, and other conditions have been determined in laboratory animals and a smaller subset has been identified in humans.";

paragraph 9 ("Chronic diseases, including obesity, Alzheimer's, diabetes, cardiovascular diseases, and certain cancers (among others), are generally produced by the interplay of environmental factors and genetic mechanisms.");

and paragraph 23 ("Similar strategies of identifying known pathways, known genes, and known enzymes as drug targets are used for almost all major diseases including Alzheimer's, cancer, diabetes, and obesity.").

No new matter is added by these amendments.

In view of the above reasoning, it is hoped that the claims are now in a condition for allowance.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-752-4085.

Deposit Account

The Commissioner is hereby authorized to charge any calculated fee or any additional fees associated with this communication in particular and this application in general, and to credit any overpayment to Bell & Associates Deposit Account No. 50-3194.

Respectfully submitted,

Adam W. Bell, Reg. No. 43,490
BELL & ASSOCIATES
58 West Portal Avenue # 121
San Francisco, California 94127 USA
Tel: (415) 752-4085 ~ Fax: (415) 276-6040
info@bell-iplaw.com ~ www.bell-iplaw.com